Are Outcomes from Severe Acute Kidney Injury Really Improving?

Acute kidney injury (AKI) is a common complication of critical illness, affecting nearly two-thirds of patients admitted to intensive care units (ICUs) (1–3). Sepsis is one of the most commonly identified etiologies for AKI (4), so as incidence rates for sepsis climb (5), we might expect to see the same for AKI. Equally, as overall outcomes for sepsis improve, outcomes for AKI should also be steadily improving. Forget about finding a specific treatment for either one, we are stamping out this disease without even understanding how!

There is an old saying: "if it seems too good to be true, it probably is." Are we deceiving ourselves? Is it really credible to think that despite ever-increasing incidence and no new breakthroughs in therapy, outcomes are really improving so dramatically? One place to aim our scrutiny is detection rates. The intensive care community has been beating the drum for some time now that both sepsis and AKI are underdiagnosed (6, 7). A natural consequence of these efforts is that detection rates should increase; and not only should they increase, but the increase should come mainly from less severe (less obvious) cases. As a result, survival should improve merely as we increase the denominator with less critical patients. However well investigators control for this fact using statistical risk adjustment, some level of detection bias is undoubtedly in play. This is particularly true when we use administrative databases with *International Classification of Diseases, 9th Revision* (ICD-9), codes. Before 2005, ICD-9 coding for acute renal failure (584.X) was based on rather loose clinical criteria, and gradually, there has been increasing standardization based on consensus criteria as these have become available (8, 9). Thus, comparing the incidence of AKI based on ICD-9 coding from, for example, 2000 to 2009 would be dramatically affected by changes in coding practice. A similar situation exists with sepsis, as new ICD-9 codes were added in 2002 and 2003.

Nevertheless, even when clinical criteria are used to define sepsis (5) or AKI (10), there is evidence of changing incidence and outcomes. Using international guidelines for diagnosis, Kaukonen and colleagues (5) found that comparing 2000 and 2012, there was an increase in the proportion of patients admitted to the ICU with sepsis, going from 7.2% to 11.1% (odds ratio, 1.54; 95% confidence interval [CI], 1.47–1.61). However, during this same period, there was an annual decrease in hospital mortality of 1.3% and a relative risk reduction of 47.5% (95% CI, 44.1–50.8%). In adjusted analyses, mortality decreased throughout this period, with an odds ratio of 0.49 (95% CI, 0.46–0.52) in 2012 compared with 2000 ($P < 0.001$). Similarly, Bagshaw and colleagues (10) found that the incidence of AKI (defined using creatinine and urine output) during the first 24 hours of ICU admission progressively increased from 1996 to 2005, and yet associated mortality decreased.

In this issue of the *Journal*, Sakhuja and colleagues (pp. 951–957) examined the incidence and outcomes for patients receiving dialysis for sepsis-associated AKI and found an increase in both incidence and survival (11). Although these authors did rely on billing codes, the accuracy for AKI receiving dialysis tends to be quite high. Thus, it is unlikely to be explained by detection bias. Given the findings of Kaukonen and colleagues (5) and Bagshaw and colleagues (10), these results are perhaps not surprising, but what could be the explanation? One possibility is that physicians are simply providing dialysis to more patients than they used to, and this increase has occurred in the less severe end of the spectrum. Similarly, in the case of sepsis, perhaps physicians are admitting more low-risk patients with sepsis to the ICU. After all, the use of dialysis or the ICU is subjective for some patients. Although Sakhuja and colleagues used the term "requiring dialysis," what they actually studied was patients receiving dialysis (11). If we simply provide dialysis or ICU care for less severe patients, average outcomes for all patients receiving dialysis or ICU care should improve.

However, this explanation is not supported by the analyses performed in studies by Sakhuja (11) and Kaukonen (5). Authors in both studies used multivariate modeling to control for underlying disease severity and still found improving outcomes over time. If outcomes for sepsis and AKI are truly improving, might this be because of better care? The most important change in care of patients with sepsis has been the use of a bundle of resuscitation treatments known as "early goal-directed therapy." However, recent large trials from the around the world have failed to show improved outcomes with this bundle (12). For AKI receiving dialysis, timing, dose, and type of therapy (continuous vs. intermittent) are potentially important, but despite multiple studies, there is insufficient evidence that any of these affects short-term survival. Importantly, the annual decline in mortality in the study by Kaukonen did not differ significantly between patients with severe sepsis and those with all other diagnoses (OR, 0.94 [95% CI, 0.94–0.95] vs. 0.94 [95% CI, 0.94–0.94]; $P = 0.37$). So perhaps improvements in outcome for sepsis and AKI are coming from better overall outcomes for critically ill patients.

This explanation, if true, would be perfectly acceptable, but there is reason to believe that something else is also happening. Over time, patients cared for in the ICU are increasingly being discharged to long-term care facilities (5). For patients with septic shock, mortality at hospital discharge may be less than 20%, but it is still greater than 40% at 1 year (12). These figures are quite similar to stage 2–3 AKI in the setting of community-acquired pneumonia (13). Indeed, even mild AKI has an effect on survival as far out as 10 years (14), and we do not have clear evidence these statistics are improving. Finally, long-term outcomes from AKI include not only survival but also renal recovery. After an episode of AKI receiving dialysis, less than 40% of patients are alive and free of dialysis at 1 year (15).

In conclusion, we can be satisfied that there is robust evidence that hospital survival rates are improving for patients with sepsis-induced AKI, even those receiving dialysis. However, increasingly, hospital survival is a poor surrogate for long-term

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survival. Long-term survival remains poor; it is worse than many forms of cancer. When survival and recovery after AKI are improving over the long term, we can truly rejoice. ■

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Identification of Sepsis among Ward Patients

Sepsis is a systemic response to infection, which may progress to severe sepsis and septic shock (1). It is a global health problem that carries a huge economic burden (2, 3). The last decade has seen a significant drive to improve outcomes for patients with sepsis, with substantial effort focused on intensive care unit (ICU) and emergency department (ED) patients in particular. Recent data have indicated that ward patients who develop sepsis have worse outcomes than ICU or ED patients (4, 5), which has led to efforts to improve sepsis recognition in the ward environment to enable prompt intervention.

Most hospitals with ward-based early sepsis recognition programs use early warning scores with track and trigger systems to identify patients at risk. Many of these tools use systemic inflammatory response syndrome (SIRS) criteria, as these physiologic variables are routinely collected during clinical/nursing care and form part of the most recent international definitions set for sepsis (6). SIRS criteria were originally proposed by Bone and colleagues (7) to describe the host response to an infection in an effort to standardize the terminology used and to improve early detection of sepsis and consistency when enrolling patients to clinical trials. Unfortunately, a SIRS response can be seen after a wide variety of insults other than infection; thus, these criteria have poor specificity for sepsis, leading some to question the value of SIRS to identify it (8–10). In this issue of the *Journal*, Churpek and colleagues (pp. 958–964) use data drawn from a Clinical Research Data Warehouse containing routine physiological monitoring and laboratory variables to evaluate the relationships among SIRS criteria, organ dysfunction, and mortality (11).

Among a cohort of almost 270,000 patients admitted to the wards of five US hospitals between 2008 and 2013, nearly half met two or more SIRS criteria simultaneously at least once during their ward admission. The cumulative proportion of patients who

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ORIGINAL ARTICLE

Acute Kidney Injury Requiring Dialysis in Severe Sepsis

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Abstract

Rationale: Understanding the changing incidence and impact of acute kidney injury requiring dialysis in patients with severe sepsis will allow better risk stratification, design of clinical trials, and guide resource allocation.

Objectives: To assess the longitudinal incidence of acute kidney injury requiring dialysis and its impact on mortality in patients with severe sepsis.

Methods: Retrospective cohort study of adults (≥20 yr) hospitalized with severe sepsis from 2000 to 2009 in the United States using a nationally representative database.

Measurements and Main Results: We calculated the incidences of acute kidney injury requiring dialysis and mortality over time. We used linear regression to assess temporal trends. We used logistic regression to estimate the odds of acute kidney injury requiring dialysis and mortality. Of the estimated 5,257,907 hospitalizations with severe sepsis, 6.1% had acute kidney injury requiring dialysis. The odds of acquiring acute kidney injury requiring dialysis increased by 14% in 2009 compared with 2000. Mortality in patients with acute kidney injury requiring dialysis was higher (43.6% vs. 24.9%; $P < 0.001$). After multivariable adjustment, odds of mortality declined 61% by the year 2009. Acute kidney injury requiring dialysis remained an independent predictor of mortality in patients with severe sepsis, although its influence on mortality declined with time.

Conclusions: Incidence of acute kidney injury requiring dialysis in patients with severe sepsis has increased over time; conversely, associated mortality has declined. The likelihood of demise from acute kidney injury requiring dialysis in patients with severe sepsis has also declined.

Keywords: acute kidney injury; dialysis; sepsis

At a Glance Commentary

Scientific Knowledge on the Subject: The incidence of severe sepsis hospitalizations has increased in the last decade, but mortality has continued to decrease. Acute kidney injury is the most common organ failure in those with severe sepsis and is associated with high mortality. Previous literature suggests that incidence of acute kidney injury is also increasing over time.

What This Study Adds to the Field: In this study using a nationally representative database we found that the incidence of acute kidney injury requiring dialysis in those with severe sepsis has increased over the last decade, but the associated mortality has declined. We also found that the odds of mortality associated with acute kidney injury requiring dialysis in those with severe sepsis have decreased over time.

Severe sepsis, the systemic inflammatory response syndrome caused by an infection in the presence of at least one organ failure, is a common and often fatal condition. Estimates of incidence have steadily risen over the past several years such that approximately 1 in 40 hospitalizations in the year 2007 were complicated by severe sepsis (1). Moreover the incidence of severe sepsis is much higher than many common diseases, such as breast cancer and HIV infection. Conversely, case

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fatality rates have improved but mortality still remains unacceptably high (~27% in 2007) (1).

Acute kidney injury (AKI) is common in patients with sepsis. Using data from the Australian New Zealand Intensive Care Society Adult Patient Database, Bagshaw and coworkers (2) reported an AKI incidence of 42.1% in patients with sepsis. Similarly, Kumar and coworkers (1) found that AKI represented the most frequent organ failure in persons with severe sepsis. Correspondingly, two multicenter studies suggested that more than 40% of all AKI in critically ill patients could be attributed to sepsis (3, 4). Similar to other illnesses, development of AKI in persons with severe sepsis independently predicts worse outcomes and is associated with increased costs (2, 5).

AKI is a broad term that represents a syndrome across a continuum of graded renal injury, the most severe of which requires intervention in the form of dialysis. Several investigations have now demonstrated a substantial rise in the incidence of AKI in different clinical settings including in critically ill patients (6, 7). However, it is unclear whether the rising incidence is caused by constant refinements in definitions and better coding practices, enhanced recognition, or both. However, we believe AKI requiring dialysis (AKI-D) would be less likely to be affected by these factors. Although it is reasonable to hypothesize that with enhanced attention to AKI, health care providers would institute measures to prevent ongoing kidney injury earlier in the course of illness thereby mitigating the need for dialysis, a recent study found that the incidence of AKI-D was rising in concert with the incidence of AKI (8). Although epidemiologic investigations have examined the occurrence and associated outcomes of AKI in persons with sepsis (2, 3), estimates of the incidence and outcomes of AKI-D and their evolution over time are currently unknown. As both severe sepsis and AKI-D are expensive, resource intensive, and associated with worse outcomes, it is important to obtain knowledge of these estimates. This would enable health care planners and policy makers to appropriately allocate resources to a large fraction of hospitalizations. Moreover, such information would be helpful in prognostication, risk stratification, and design of future clinical trials.

We therefore sought to describe AKI-D in persons with severe sepsis. The goals of our study were to determine the longitudinal incidence (years 2000–2009) of AKI-D in persons with severe sepsis and to assess the longitudinal impact of AKI-D on mortality in persons with severe sepsis during the same time period. We used a large nationally representative database maintained by the Agency of Health Care Research and Quality to enhance the external validity of our results.

Methods

Study Design and Data Source

We performed a retrospective study using national data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS). NIS is the largest all-payer inpatient care database publicly available in the United States that contains data from a 20% stratified sample of U.S. community hospitals (9). Each hospitalization is treated as an individual database entry and information regarding common demographic variables (age, race, and sex along with primary insurance, hospital characteristics), teaching status, location (rural vs. urban), size of hospital, and hospital region is available. Data from the first 10 years of this millennium (2000–2009) were used for this study. We used the provided principal diagnosis, secondary diagnoses, and procedural diagnoses associated with each hospitalization in the database for this study.

Study Population

We included hospitalizations with severe sepsis with age greater than or equal to 20 years in this study. In accordance with previous literature (1, 10) we defined severe sepsis as either use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for severe sepsis or septic shock; or use of ICD-9-CM codes for septicemia, bacteremia, or fungemia with at least one organ dysfunction. We provide detailed codes in Tables E1A and E1B in the online supplement.

We defined AKI-D using ICD-9-CM code for AKI (584.X) along with the procedure code for hemodialysis (39.95). These codes have demonstrated excellent positive and negative predictive value to identify admissions with AKI-D in administrative databases (11). We excluded patients who died within 24 hours of hospital admission because they would not have had enough time to develop AKI-D (5.5% of all severe sepsis hospitalizations). We also excluded patients on maintenance dialysis.

Study Variables

We identified demographic characteristics (age, sex, and race), hospital characteristics (teaching status, location, bed size, and region), and primary payer using appropriate variables from NIS database. We then divided hospitals into tertiles based on the yearly volume of severe sepsis discharges (<195, 195–412, >412 hospitalizations for severe sepsis per year). We used Deyo's modification of Charlson comorbidity index to identify the burden of comorbid diseases (12). We identified persons receiving mechanical ventilation using ICD-9-CM procedure codes 96.70, 96.71, and 96.72. Discharges with missing data were excluded except for race, which was missing in about 20% of discharges. We included missing race as a separate subgroup of race for analyses. Overall, less than 1% observations were excluded secondary to missing data.

Outcomes

Our primary outcomes of interest were all-cause in-hospital mortality and the independent influence of AKI-D on mortality in those with severe sepsis. We also assessed the longitudinal incidence of AKI-D in those with severe sepsis from the years 2000–2009. During the same time period we also report the longitudinal risk of acquiring AKI-D and the longitudinal impact of AKI-D on mortality.

Statistical Analysis

We performed all statistical analysis using STATA 13.1 (College Station, TX). Using the weights provided in NIS database, we generated national estimates for the number of overall severe sepsis hospitalizations and hospitalizations in each age category (20–44, 45–64, 65–79, and ≥80 yr) and sex. We used chi-square test to compare categorical

variables and linear regression to assess significance of trends over time.

We used multivariable logistic regression model to estimate odds of AKI-D and odds of all-cause inpatient mortality. All clinically relevant variables were included in the final multivariable models that were adjusted for age, sex, race, primary payer, Charlson score, hospital teaching status, hospital location, hospital region, hospital volume (small, medium, and large), hospital bed size, individual organ dysfunctions, mechanical ventilation use, and year of admission. The model with mortality as dependent variable was also adjusted for AKI-D as a predictor variable. To assess if there is a differential effect of year on mortality between those with AKI-D and those without we checked for an interaction between AKI-D status and year. We then used linear combination of estimates to determine the independent effect of AKI-D on mortality for each individual year studied.

As characteristics of those with AKI-D were different from those without AKI-D, we used a propensity score matching approach to adjust for differences in the two cohorts. We used a multivariable logistic regression model to calculate the likelihood that a person with severe sepsis would develop AKI-D. This model included factors that might result in AKI-D regardless of their individual statistical significance. Each hospitalization in the AKI-D group was then matched with the hospitalization in the non–AKI-D group using 1:1 nearest neighbor matching with 0.01 calipers and without replacement. The final matched cohort had 65,833 matched pairs (total of 131,666 observations). All baseline variables had standardized differences less than 10% (*see* Figure E1) after propensity matching. Sandwich covariance estimator was used to adjust for correlation between matched pairs in the logistic regression model in propensity-matched sample.

To better understand the effects of readmissions on our results we performed an additional sensitivity analysis where potential multiple admissions of same patient were identified using hospital records with similar age, sex, race, primary payer, hospital identification code, and year of admission. This technique has been previously used to identify potential readmissions using the NIS database (13, 14). We then restricted our analyses to the cohort with unique observations and excluded any duplicate observations. We assessed the odds for AKI-D, mortality, and independent effect of AKI-D on mortality for each individual year using regression models as for the original cohort of patients.

Table 1. Baseline Characteristics of Patients with and without Acute Kidney Injury Requiring Dialysis

Characteristic	AKI-D (%) (*n* = 323,120)	Without AKI-D (%) (*n* = 4,934,787)	*P* Value
Age group			
20–44	10.9	9.4	<0.001
45–64	35.3	27.7	
65–79	36.7	33.9	
⩾80	17.1	29.0	
Sex			
Male	57.7	50.0	<0.001
Race/ethnicity			
White	51.7	55.4	<0.001
Black	15.6	11.3	
Hispanic	9.4	7.0	
Asian	2.4	2.1	
Native American	0.5	0.4	
Others	2.7	2.1	
Missing	17.5	21.6	
Primary payer			
Medicare	58.3	65.8	<0.001
Medicaid	12.6	10.3	
Private	22.8	18.4	
Self-pay	3.4	3.0	
No charge	0.3	0.3	
Other	2.3	2.3	
Charlson score			
<3	63.0	74.1	<0.001
3–4	23.5	15.1	
⩾5	13.5	10.9	
Respiratory dysfunction	64.7	46.8	<0.001
Cardiovascular dysfunction	43.3	35.9	<0.001
Hepatic dysfunction	13.0	4.9	<0.001
Renal dysfunction	100.0	45.7	<0.001
Hematologic dysfunction	25.1	17.7	<0.001
Metabolic dysfunction	28.1	14.7	<0.001
Neurologic dysfunction	13.7	12.2	<0.001
Septic shock	43.3	35.9	<0.001
Mechanical ventilation use	56.1	34.2	<0.001
Hospital teaching status			
Teaching	53.3	45.5	<0.001
Hospital bed size			
Small	8.6	11.1	<0.001
Medium	22.2	24.6	
Large	69.2	64.3	
Hospital volume			
Small	25.2	33.4	<0.001
Medium	36.1	34.0	
Large	38.8	32.7	
Hospital location			
Urban	95.7	89.8	<0.001
Year of admission			
2000	4.3	5.0	<0.001
2001	4.9	5.6	
2002	6.2	6.5	
2003	7.4	7.5	
2004	8.8	9.0	
2005	10.5	10.3	
2006	11.5	11.5	
2007	13.0	13.0	
2008	15.9	15.3	
2009	17.3	16.1	

Definition of abbreviation: AKI-D = acute kidney injury requiring dialysis.

Results

Patient Characteristics and Incidence of AKI-D

There were an estimated 5,257,907 (95% confidence interval [CI], 5,048,945–5,466,869) hospitalizations with severe sepsis over the study period. Of those, estimated 323,120 (95% CI, 305,522–340,717) had AKI-D for an overall crude cumulative incidence of 6.1%. AKI-D was seen less often in those aged 80 years or older (17.1% vs. 29%) (Table 1). Persons developing AKI-D were more often males, and were more likely to be admitted to teaching hospitals, hospitals with larger bed sizes, and hospitals with higher volumes of severe sepsis (Table 1). Persons with AKI-D were also more likely to require mechanical ventilation (56.1% vs. 34.2%; $P < 0.001$), have septic shock (43.3% vs. 35.9%; $P < 0.001$), and have other organ dysfunctions than those without AKI-D (Table 1).

Trends of AKI-D

The proportion of patients with severe sepsis who developed AKI-D steadily rose over the time period of study (5.2% in 2000 and 6.6% in 2009) with an annualized increment of 2.1% (Figure 1A). This increase was consistent across all age groups as well as sex, although the rise did not meet statistical significance in the age group greater than or equal to 80 year old (Figures 1B and 1C). In adjusted analyses, after accounting for potential confounding variables, the odds of acquiring AKI-D in those with severe sepsis increased by 14% (Figure 2A).

Outcomes

The overall all-cause inpatient mortality for those with severe sepsis was 26.1%. Crude mortality in persons with AKI-D was significantly higher than those without AKI-D (43.6% vs. 24.9%; $P < 0.001$). Despite lower incidences of AKI-D in the cohort aged 80 years and older, overall crude mortality and crude mortality in people developing AKI-D was significantly higher in this cohort (Figure 3A). Mortality was also higher in males in both overall and AKI-D cohorts (Figure 3B).

There was a steady decline in overall case fatality rates and case fatality rates in the cohort acquiring AKI-D (Figure 1A). However, the magnitude of this decline was approximately half that observed in the entire cohort (19.2% vs. 41.6%). Decrements in mortality rates were observed across all age categories and sex (Figures 3A and 3B).

On multivariable analysis, the odds of mortality for persons with severe sepsis declined by 61% from 2000 to 2009 (odds ratio [OR], 0.39; 95% CI, 0.37–0.41) (Figure 2A). After adjustment for potential

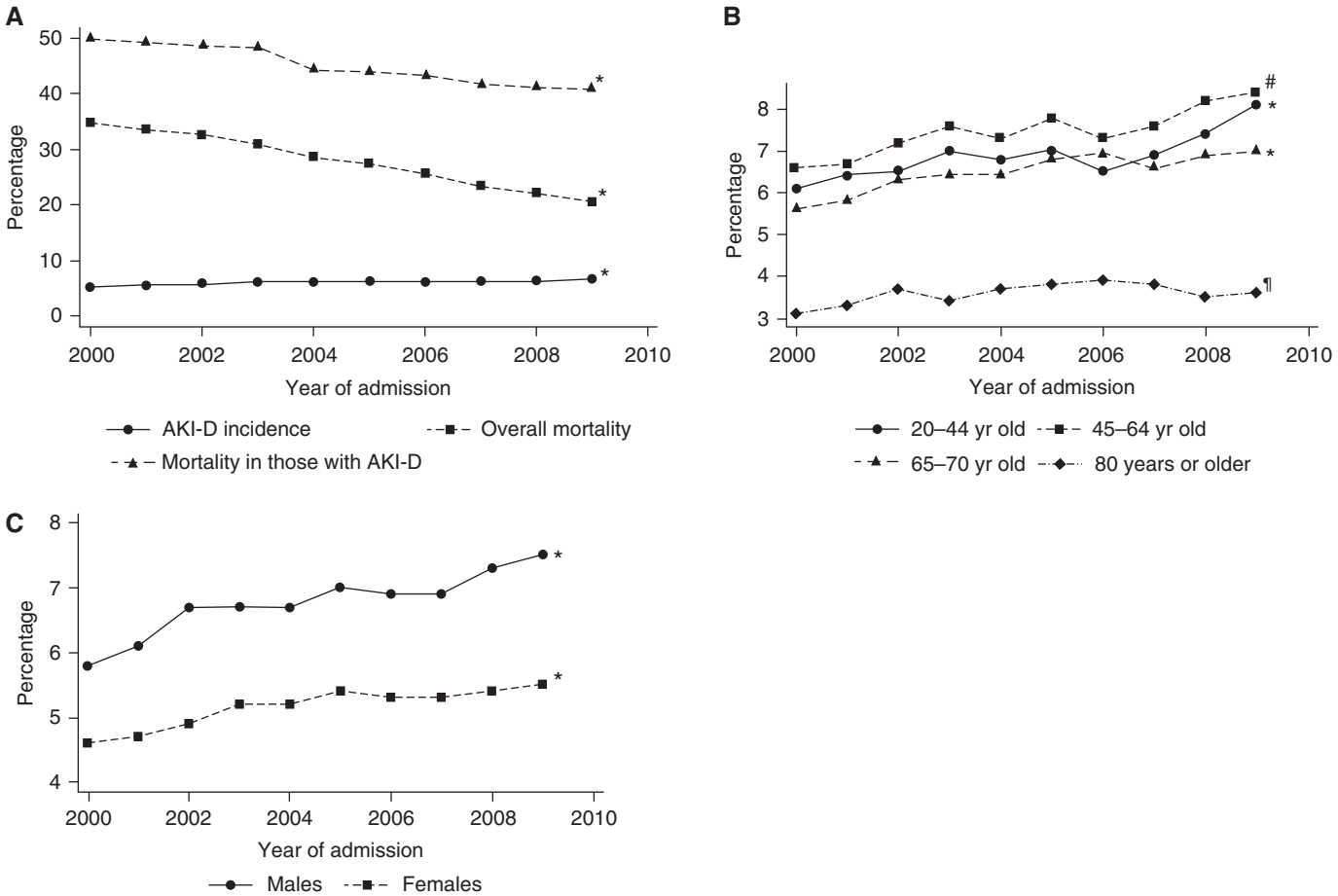

Figure 1. Incidence of acute kidney injury requiring dialysis (AKI-D) and mortality in those admitted with severe sepsis. (*A*) Incidence of AKI-D and mortality over time. (*B*) Incidence of AKI-D by age group over time. (*C*) Incidence of AKI-D by sex over time. *$P < 0.001$; #$P = 0.003$; ¶$P = 0.07$.

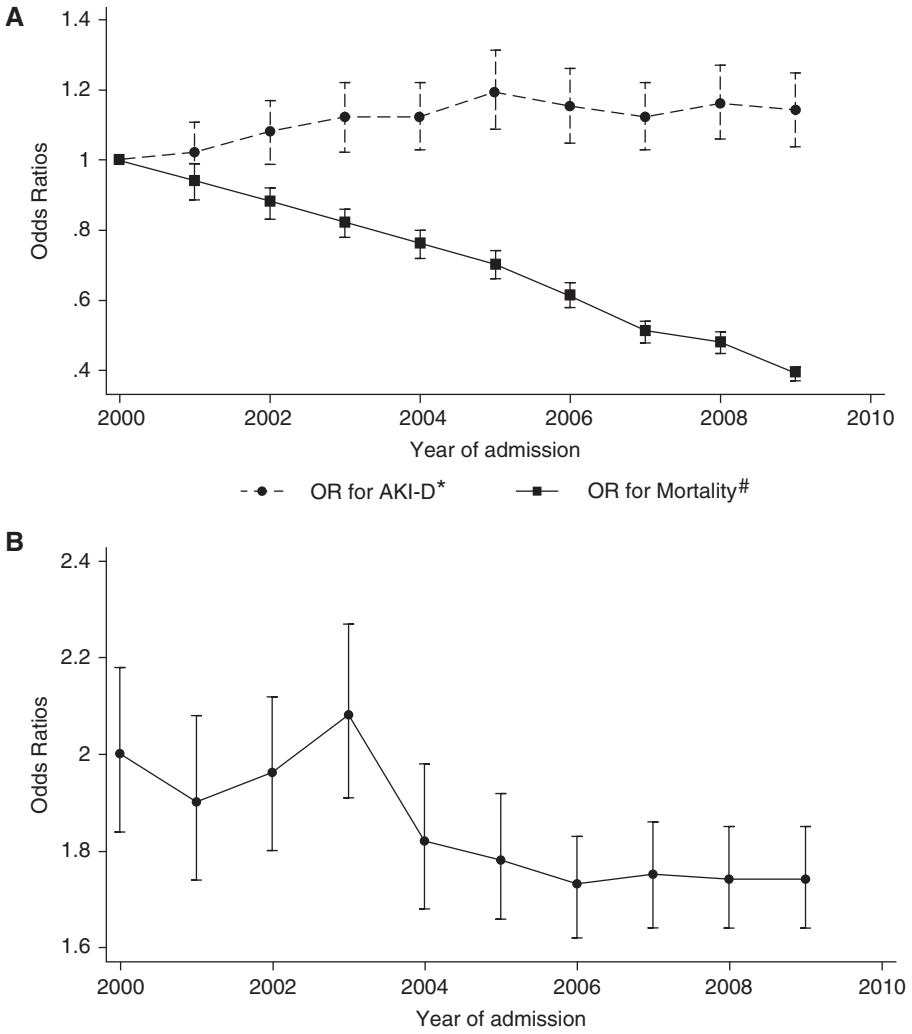

Figure 2. Odds for developing acute kidney injury requiring dialysis (AKI-D) and mortality. (*A*) Odds for developing AKI-D and mortality over time. *Adjusted for age, sex, race, primary payer, Charlson score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use, and year of admission. #Adjusted for age, sex, race, primary payer, Charlson score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, AKI-D status, mechanical ventilation use, year of admission, and interaction between AKI-D status and year of admission. (*B*) Odds of mortality due to AKI-D over time. Adjusted for age, sex, race, primary payer, Charlson score, hospital teaching status, hospital location, hospital region, hospital volume, hospital bedsize, individual organ dysfunctions, mechanical ventilation use, and year of admission. OR = odds ratio.

confounding factors, AKI-D remained an independent predictor of in-hospital mortality. In the year 2000, the odds of mortality in those with severe sepsis who developed AKI-D were twice than those who did not have AKI-D (OR, 2.00; 95% CI, 1.84–2.18). These odds of mortality declined as evidenced by significant interaction term between year of admission and AKI-D (interaction $P = 0.002$) but still remained significant during the time period of our study, such that by the year 2009 the odds of mortality in those with AKI-D were 1.74 times (OR, 1.74; 95% CI, 1.64–1.85) (Figure 2B).

On propensity-matched analysis, our results were similar. AKI-D remained an independent predictor of mortality with OR 1.78 (95% CI, 1.59–2.00) in the year 2000. Overall odds of mortality in persons with severe sepsis decreased by 64% from 2000 to 2009 (*see* Figure E2A) and impact of AKI-D on mortality also decreased with time (interaction $P = 0.01$) (*see* Figure E2B). We observed similar trends for odds of AKI-D, mortality (*see* Figure E2C), and impact of AKI-D over time (interaction $P < 0.001$) (*see* Figure E2D) when only unique observations were analyzed.

Discussion

We show that although the incidence of AKI-D complicating severe sepsis is rising, the associated mortality is declining. These findings were remarkably similar across age groups and sex. We found that after adjustment for confounding variables, the risk of developing AKI-D complicating severe sepsis in 2009 was 14% higher than that in 2000. Conversely, the risk of AKI-D on mortality from severe sepsis was 61% lower in 2009 relative to 2000. Our results for mortality and the declining impact of AKI-D on mortality were similar when we adjusted for the likelihood that people with severe sepsis would acquire AKI-D and matched people who acquired AKI-D to people who were AKI-D free.

Our results are in agreement with earlier reports demonstrating increasing incidences of AKI with time (6, 8, 15, 16). Our study can be most readily compared with the study by Bagshaw and coworkers (6), which examined the incidence and outcomes of AKI in all intensive care unit admissions using Australian New Zealand Intensive Care Society Adult Patient Database. These authors used an acute serum creatinine elevation to greater than or equal to 1.5 mg/dl and urine output less than 410 ml in 24 hours to define AKI. They found that although the incidence of AKI progressively increased over the study period that extended from 1996 to 2005, associated mortality decreased. These authors, however, only accounted for patients who developed AKI during the first 24 hours of intensive care unit admission and were unable to provide estimates of acute renal-replacement therapy. In contrast we restricted our attention to AKI requiring dialysis, thereby capturing a population that may have developed AKI several days after hospital admission. Moreover using our scheme of patient inclusion (AKI and the need for renal-replacement therapy), we probably mitigated influences that may artificially inflate the incidence of AKI secondary to heightened awareness and more complete capture from proper coding practices.

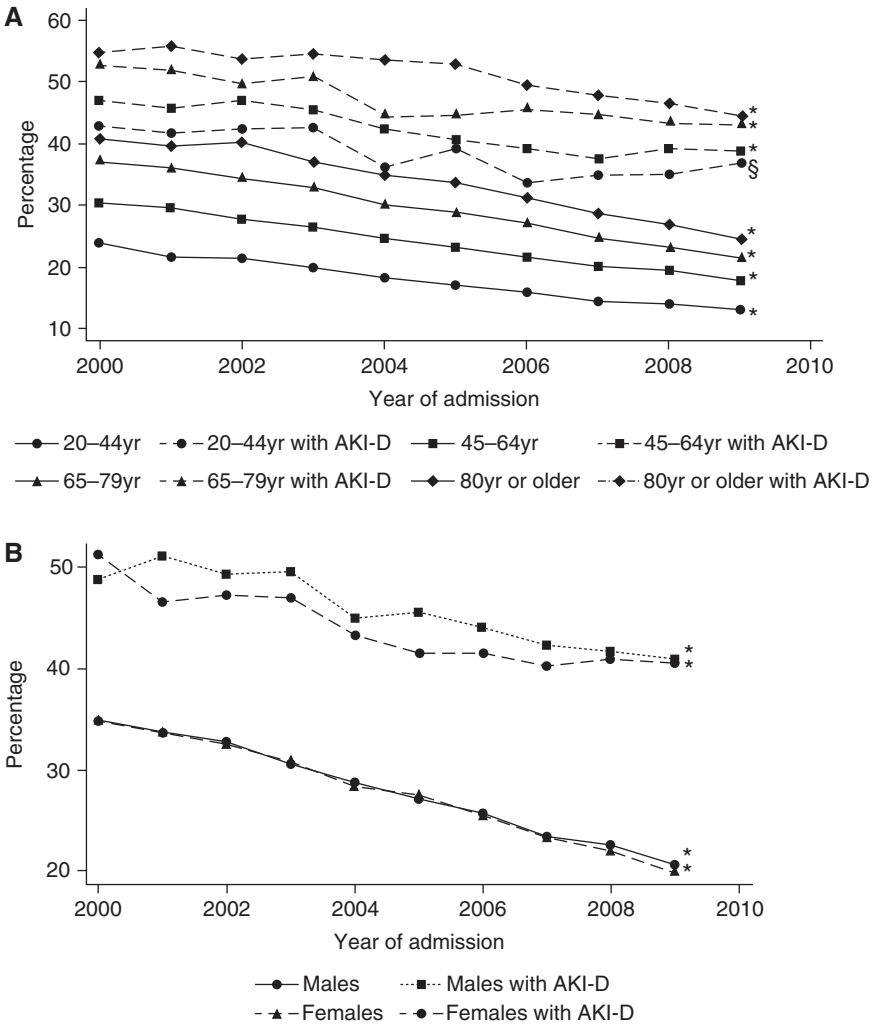

Figure 3. Age- and sex-specific mortality in those admitted with severe sepsis. (*A*) Mortality by age group in overall cohort and those with acute kidney injury requiring dialysis (AKI-D). (*B*) Overall mortality by sex in overall cohort and those with AKI-D. *$P < 0.001$; §$P = 0.004$.

More recently, Hsu and coworkers (8) used the NIS database to estimate the national incidence and trends of AKI-D in all hospitalizations over the last decade and found that the population incidence rate increased from 222 to 533 cases per million person-years. They also found that mortality declined from 29.1% in 2000 to 23.5% in 2009. In addition, they showed that the odds of AKI-D increased by 7% annually (OR, 1.07; 95% CI, 1.06–1.07) on adjusted analysis. In our study, using year as a continuous variable, we found a 1% increase in annual odds (OR, 1.01; 95% CI, 1.00–1.01) of AKI-D in those with severe sepsis (results not shown). Differences in these results are likely caused by different populations studied; Hsu and coworkers (8) included all hospital admissions but we restricted our sample to those greater than or equal to 20 years with severe sepsis that survived the first day of hospitalization. In addition, we performed much more rigorous adjustments to the logistic regression model than the previous study.

We also found that those with severe sepsis aged 80 years or older had lower incidence and risk of AKI-D even on adjusted analysis. These findings may reflect physician, patient, and/or family preferences to not initiate renal-replacement therapy in the very elderly; a hypothesis supported by the fact that the highest incidence of all AKI occurred in those aged 80 years or older (53.0% vs. 50.1% in 65–79 yr vs. 47% in 45–64 yr vs. 39.2% in 20–44 yr; $P < 0.001$).

Our data sources do not provide a ready explanation for the increasing incidence of AKI-D and improving mortality. The increasing incidence of AKI-D could reflect the overall increasing complexity of patients with severe sepsis as was shown by Kumar and coworkers (1). Progressively earlier initiation of dialysis for AKI in those with severe sepsis is potentially another explanation for these results. In addition, increased investigative procedures using iodinated contrast in the form of computed tomography scans could also contribute to the same, although it is difficult to capture and thus study their impact reliably using ICD-9-CM codes. The outcomes for severe sepsis have improved since early part of last decade, which has been thought to be caused by better understanding of the pathophysiology of severe sepsis and improved care of patients. The improvement in mortality in those with AKI-D is likely a reflection of overall improvement in care of patients with severe sepsis.

Although we have used a robust, nationally representative database, our study has important limitations. There is no consensus definition of severe sepsis for studies in administrative databases. Although we have used severe sepsis and organ failure codes in accordance with previous studies (1, 10) they may not reliably identify those with severe sepsis. Constant evolution in ICD-9-CM codes, particularly addition of codes for severe sepsis in 2002 and septic shock in 2003, may have also impacted our results but we did see a consistent trend across many years of the study. The NIS database has incomplete data regarding race of admissions, thus limiting us in being able to interpret and comment on the racial incidence, impact, and trends of AKI-D.

Our data source also limited us from identifying outcomes post hospital discharge. As such our results of improvements in mortality may simply reflect a shift from in-patient mortality to demise post-discharge. In addition, each hospitalization is treated as a separate observation in NIS database with no variables to help uniquely identify readmissions. We attempted, however, to exclude potential readmissions by identifying unique observations using patient characteristics, primary payer hospital identification, and year of admission and found similar trends in that

cohort which lends credence to our results. Finally, certain variables, such as estimated glomerular filtration rate values, which accurately identify levels of preexisting renal dysfunction, were unavailable in our data source, which limits our ability to discern the impact of advanced degrees of renal dysfunction on the decision to initiate dialysis.

The main strength of our study is the use of a large nationally representative database that allows for easily generalizable and accurate estimates to be generated. An additional strength is the use of propensity score matching to make the groups with and without AKI-D similar in baseline characteristics for further analyses. The fact that our results showed similar trends in overall, propensity-matched sample and sample with only unique observations argues for the robustness of our results.

To summarize, using a nationally representative and well-characterized database we show that even though the incidence of AKI-D is progressively rising in those with sever sepsis, the impact of AKI-D on mortality is decreasing. Nevertheless, AKI-D still remains a significant predictor of mortality in those with severe sepsis. Further studies are needed to understand the reasons behind rising incidence of AKI-D and efforts need to be targeted toward mitigating the incidence. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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